

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
13 March 2003 (13.03.2003)

PCT

(10) International Publication Number  
**WO 03/020707 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 261/20**,  
A61K 31/42, A61P 25/18

Solothurnerstrasse 87, CH-4053 Basel (CH). **YIN, Hequn**  
[CN/US]; 1306 Grandview Court, Whippany, NJ 07981  
(US).

(21) International Application Number: PCT/EP02/09700

(74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

(22) International Filing Date: 30 August 2002 (30.08.2002)

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(26) Publication Language: English

(30) Priority Data:  
60/316,390 31 August 2001 (31.08.2001) US

(84) Designated States (*regional*): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

(71) Applicant (*for all designated States except AT, US*): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

**Published:**  
— with international search report

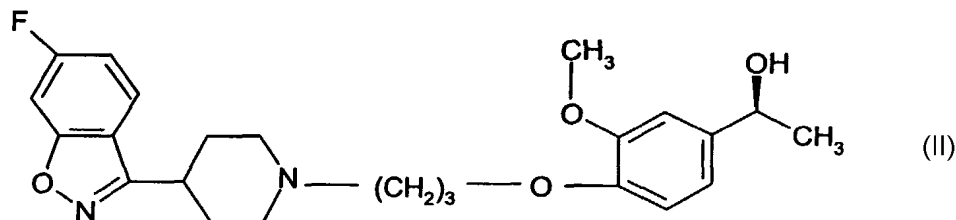
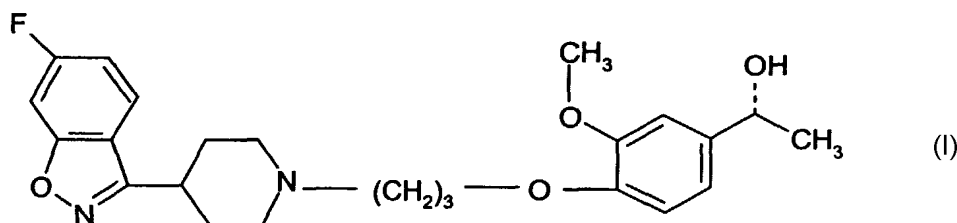
(71) Applicant (*for AT only*): **NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H.** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(75) Inventors/Applicants (*for US only*): **GRIMLER, Dominique** [FR/FR]; 14, rue des Bûcherons, F-68560 Hirsingue (FR). **KALKMAN, Hans, O.** [NL/CH];

(54) Title: OPTICAL ISOMERS OF AN ILOPERIDONE METABOLITE



(57) Abstract: The invention provides compounds of formulae (I) and (II), their preparation and their use as pharmaceuticals.



WO 03/020707 A1

- 1 -

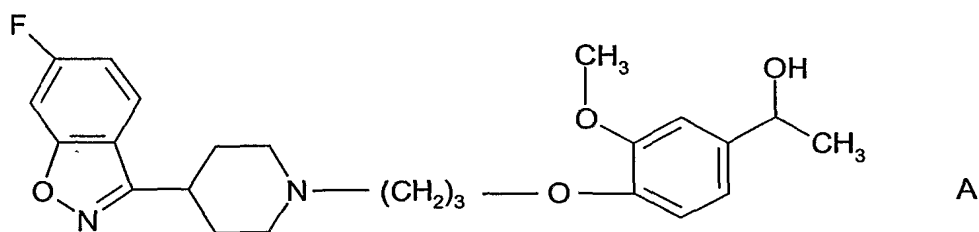
Optical isomers of an lloperidone metabolite

The present invention relates to novel isomers of a metabolite of lloperidone, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly, the invention relates to optical isomers of the metabolite P-88-8991 of lloperidone.

lloperidone is an atypical antipsychotic developed for the treatment of schizophrenia, having functional affinity for noradrenergic, dopaminergic and serotonergic receptors. See for example Richelson E. and Souder T., Life Sciences, 68:29-39 (2000).

P-88-8991 is a major circulating metabolite of lloperidone in human plasma, having the formula A

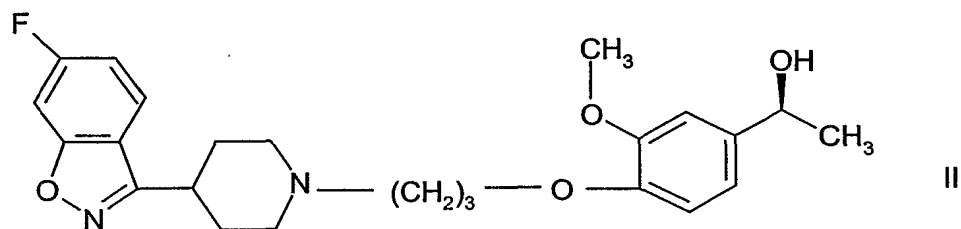
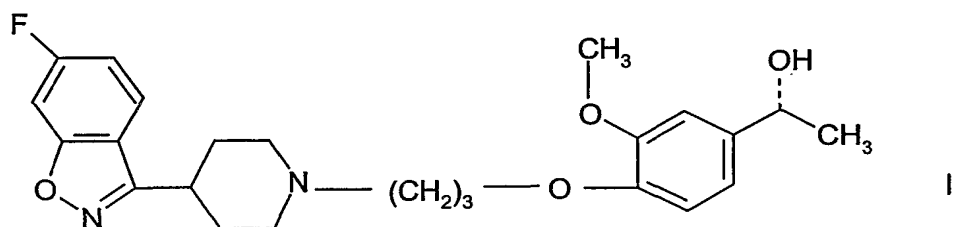


See for example Mutlib AE et al., Drug Metab. Dispos; 23(9):951-964 (1995). P-88-8991 has been shown to have plasma levels in human about 1.5 fold higher than the parent drug. It is roughly as active as lloperidone.

P-88-8991 consists of a mixture of two enantiomers which have never been disclosed in the literature. It has now surprisingly been found that humans produce only one enantiomer stereospecifically following administration of lloperidone.

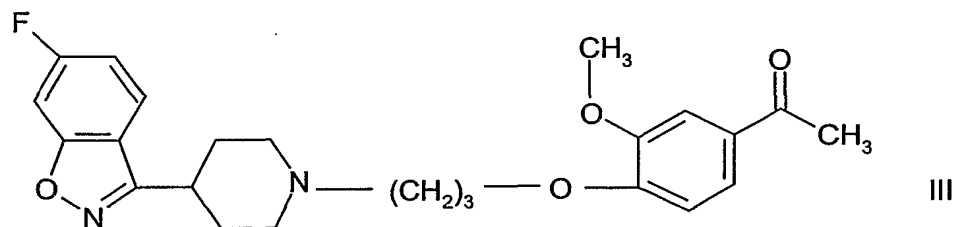
In the first aspect, the invention provides the enantiomers (R)-P-88-8991 and (S)-P-88-8991 of formulae I and II

- 2 -

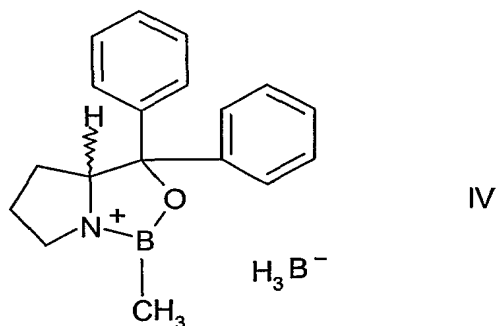


in free base or acid addition salt form.

In a further aspect, the invention provides a process for the production of the compounds of formulae I and II, comprising the reduction of lloperidone of formula III

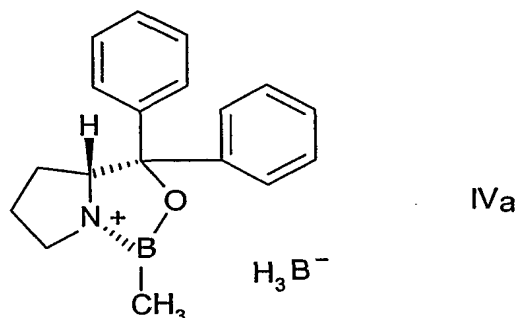


with an optically active boran complex of formula IV

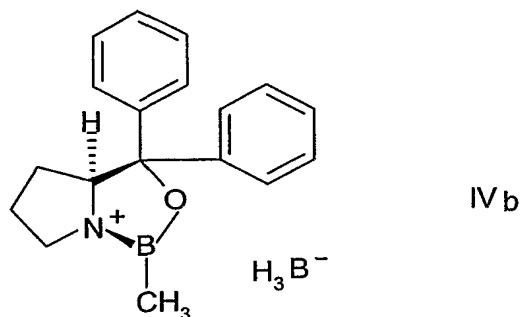


The compound (S)-1-(4-(3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy)-3-methoxy-phenyl)-ethanol of formula I is obtained using the boran complex of (3aR, 7R)-1-

methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole of formula IVa



whereas the compound (R)-1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]propoxy}-3-methoxy-phenyl)-ethanol of formula II is obtained using the boran complex of (3aS,7R)-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole of formula IVb



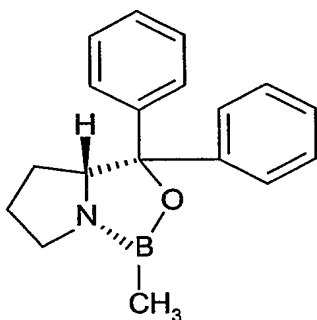
The reactions can be effected according to conventional methods, e.g. as described in the Examples.

Working up the reaction mixtures and purification of the compounds thus obtained may be carried out in accordance to known procedures.

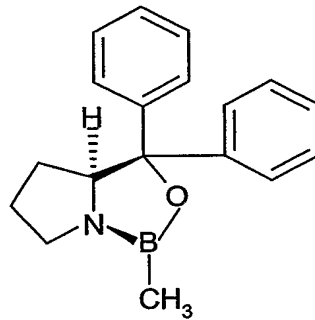
Acid addition salts may be produced from the free bases in known manner, and vice-versa. Suitable acid addition salts for use in accordance with the present invention include for example the hydrochloride.

The boran complexes used as starting materials can be produced from the corresponding compounds of formula Va and Vb

- 4 -



Va



Vb

according to known procedures, e.g. as described in the Examples.

The starting materials of formulae Va and Vb are known.

The compounds of formulae I and II and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

In particular the agents of the invention display high affinity for adrenergic  $\alpha_1$  and  $\alpha_{2c}$  receptors ( $pK_i$  8.9 and 7.8 respectively, for the compound of formula I, and 9.2 and 7.7 respectively, for the compound of formula II), high affinity for 5 HT<sub>2A</sub> and 5 HT<sub>6</sub> receptors ( $pK_i$  8.9 and 8.1 respectively, for the compound of formula I, and 8.9 and 7.8 respectively, for the compound of formula II) and moderate affinity for the D<sub>2</sub> family ( $pK_i$  7.4 to 7.6 for the compound of formula I and 7.4 to 7.8 for the compound of formula II).

Receptor affinity is determined with standard radioligand binding techniques, using human recombinant receptors and native rat brain receptors. Blockade of dopamine D<sub>2</sub> and noradrenergic  $\alpha_{2c}$  receptors is tested in cell-lines using luciferase reporter gene assays based on 2<sup>nd</sup> messenger responses.

In vivo, the agents of the invention exhibit antipsychotic activity, as assessed in standard tests such as the amphetamine-induced hypermotility and the phencyclidine-induced hyperlocomotion tests.

The amphetamine-induced hypermotility test is performed according to the method described by Arnt J in Eur. J. Pharmacol. 283, 55-62 (1995). In this test, the agents of the invention significantly inhibit the amphetamine-induced locomotion of the animals at doses of

- 5 -

about 0.01 to about 10 mg/kg s.c.

The phencyclidine-induced hyperlocomotion test is performed according to a rat adaptation of the method described by Gleason SD and Shannon HE in *Psychopharmacol.* 129, 79-84 (1997). In this test, the agents of the invention significantly block the phencyclidine-induced hyperlocomotion of the rats at doses of about 0.01 to about 10 mg/kg s.c.

The agents of the invention are therefore useful for the treatment of psychotic disorders such as schizophrenia and bipolar disorders.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 500, preferably from about 0.5 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 500, preferably from about 1 to about 300 mg of an agent of the invention, conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

The agents of the invention may alternatively be administered e.g. topically in the form of a cream, gel or the like, or by inhalation, e.g. in dry powder form.

Examples for compositions comprising an agent of the invention include, e.g. a solid dispersion, an aqueous solution, e.g. containing a solubilising agent, a microemulsion and a suspension of an agent of the invention. The composition may be buffered to a pH in the range of e.g. from 3.5 to 9.5, by a suitable buffer.

The agents of the invention can be administered either alone or in combination with other pharmaceutical agents effective in the treatment of psychotic disorders such as

- 6 -

schizophrenia or bipolar disorders. The present invention thus provides a combination comprising a therapeutically effective amount of an agent of the invention and a second drug substance, for simultaneous or sequential administration.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of psychotic disorders.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from 0.25 to about 25 mg of a compound according to the invention.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of psychotic disorders.

In still a further aspect the present invention provides a method for the treatment of psychotic disorders, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention.

Example 1(S)-1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol

56.36 g of boran complex of (3aR, 7R)-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole (1 equivalent) is dissolved under nitrogen in methylenchloride, and the solution is cooled to 0°C. A 1M solution of 1-(4-{3-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanone (iloperidone; 1 equivalent) in methylenchloride is added via a dropping funnel over 90 minutes while the internal temperature is maintained at 0°C ± 2°C. After the addition is complete, the mixture is stirred at 0°C for 20 hours. The reaction mixture is then poured into precooled methanol (0-5°C) during 1 hour. The solution is warmed to room temperature and stirred until the H<sub>2</sub> evolution ceases. The solution is concentrated by distillation and the residue dried in vacuum, treated with methanol and stirred for about 1 hour at 50°C and an additional hour at 0°C. The product is isolated by filtration and dried under reduced pressure for 3 hours at 50°C. The title compound is obtained (white crystals).

$[\alpha]_D^{20} - 19.3^\circ$  (c=1 in chloroform)

Mp: 138.2 – 138.8°C

The boran complex used as starting material can be obtained as follows:

200 ml of a solution of (3aR, 7R)-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole (1M in toluene) is stirred at room temperature under nitrogen. 1.2 equivalent borane-dimethylsulfide complex is added with a syringe. The solution is stirred for 2 further hours at room temperature. The borane complex is then crystallised by addition of 4 vol dry hexane and cooling to -12°C for 1.5 hour. The product is isolated by filtration in a sintered glass funnel and dried in vacuum at 40°C. The boran complex is obtained (white crystals).



Example 2

(R)-1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol

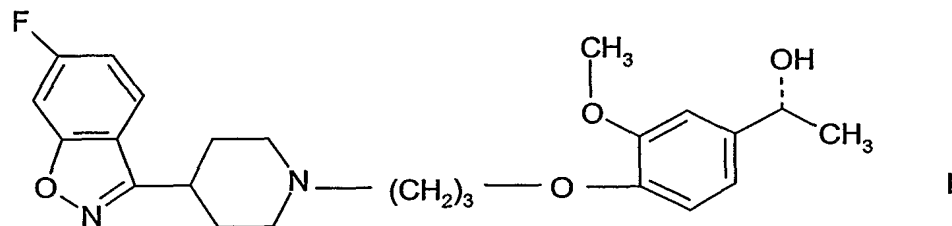
This compound is produced in analogy to Example 1, using boran complex of (3aS, 7R)-1-methyl-3,3-diphenyl-tetrahydro-pyrrolo[1,2-c][1,3,2]oxazaborole.

$[\alpha]_D^{20} = + 18.4^\circ$  (c=1 in chloroform)

Mp: 137.9 – 138.3°C

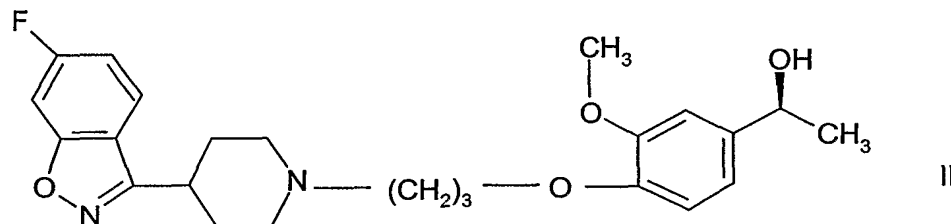
CLAIMS

1. (R)-1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol of formula I



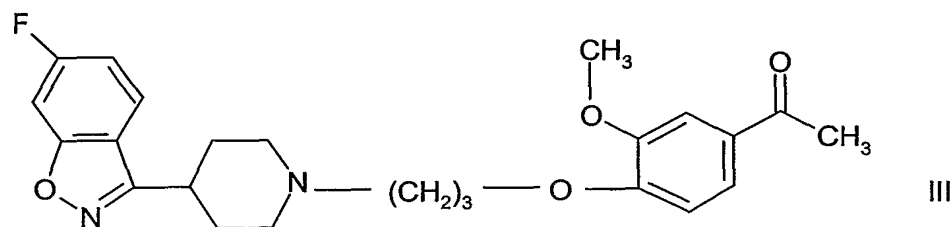
in free base or acid addition salt form.

2. (S)-1-(4-{3-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-propoxy}-3-methoxy-phenyl)-ethanol of formula II



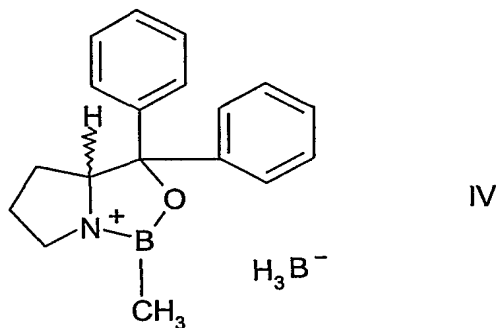
in free base or acid addition salt form.

3. A process for the production of the compounds of formulae I and II according to claims 1 and 2, and their salts, comprising the reduction of lloperidone of formula III



with an optically active boran complex of formula IV

- 10 -



and recovering the resulting compound in free base or acid addition salt form.

4. A compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.
5. A compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of psychotic disorders.
6. A pharmaceutical composition comprising a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.
7. The use of a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of psychotic disorders.
8. The use of a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of psychotic disorders.
9. A method for the treatment of psychotic disorders in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form.

- 11 -

10. A combination comprising a therapeutically effective amount of a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, and a second drug substance, for simultaneous or sequential administration.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 02/09700

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D261/20 A61K31/42 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP 0 402 644 A (HOECHST ROUSSEL PHARMA) 19 December 1990 (1990-12-19) page 27; example 9	1-10
X,Y	STRUPCZEWSKI J T ET AL: "3-(ARYLOXY)ALKYLPiPERIDiNYL-1,2-BENZISOXA ZOLES AS D2/5-HT2 ANTAGONISTS WITH POTENTIAL ATYPICAL ANTIPSYCHOTIC ACTIVITY: ANTIPSYCHOTIC PROFILE OF ILOPERIDONE (HP 873)" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, no. 7, 1995, pages 1119-1131, XP000941571 ISSN: 0022-2623 table 3, entry 56	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "G" document member of the same patent family

Date of the actual completion of the international search

27 November 2002

Date of mailing of the international search report

06/12/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Steendijk, M

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 02/09700

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MUTLIB A E ET AL: "Picogram determination of iloperidone in human plasma by solid-phase extraction and by high-performance liquid chromatography-selected-ion monitoring electrospray mass spectrometry" JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL APPLICATIONS, ELSEVIER SCIENCE PUBLISHERS, NL, vol. 669, no. 2, 21 July 1995 (1995-07-21), pages 237-246, XP004043810 ISSN: 0378-4347 abstract</p>	1,2
Y	<p>COREY E J ET AL: "A STABLE AND EASILY PREPARED CATALYST FOR THE ENANTIOSELECTIVE REDUCTION OF KETONES. APPLICATIONS TO MULTISTEP SYNTHESSES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 109, no. 25, 8 December 1987 (1987-12-08), pages 7925-7926, XP000652664 ISSN: 0002-7863 the whole document</p>	3

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/09700

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0402644	A	19-12-1990	
		AT 126512 T	15-09-1995
		AU 640653 B2	02-09-1993
		AU 5577090 A	22-11-1990
		CA 2017193 A1	19-11-1990
		CN 1305812 A	01-08-2001
		CN 1048037 A ,B	26-12-1990
		CZ 9002425 A3	12-03-1997
		DE 69021645 D1	21-09-1995
		DE 69021645 T2	22-02-1996
		DK 402644 T3	02-01-1996
		EP 0402644 A1	19-12-1990
		ES 2076253 T3	01-11-1995
		FI 104072 B1	15-11-1999
		FI 991869 A	02-09-1999
		GR 3017447 T3	31-12-1995
		HK 1006710 A1	12-03-1999
		HU 58720 A2	30-03-1992
		HU 9500576 A3	28-12-1995
		IE 68431 B1	12-06-1996
		IL 94425 A	27-02-1994
		JP 1931594 C	12-05-1995
		JP 3063263 A	19-03-1991
		JP 6062580 B	17-08-1994
		KR 157308 B1	16-11-1998
		NO 902214 A ,B,	20-11-1990
		NZ 233710 A	26-05-1992
		PH 30431 A	09-05-1997
		PL 285247 A1	11-02-1991
		PT 94084 A ,B	08-01-1991
		RU 2147583 C1	20-04-2000
		SK 242590 A3	04-11-1998
		RU 2062776 C1	27-06-1996
		US RE37029 E1	23-01-2001
		US RE37478 E1	18-12-2001
		US RE37729 E1	04-06-2002
		US 5658911 A	19-08-1997
		US 5776963 A	07-07-1998
		US 5550130 A	27-08-1996
		US 5629326 A	13-05-1997
		US 5977140 A	02-11-1999
		US 5977113 A	02-11-1999
		US 5552414 A	03-09-1996
		US 5612342 A	18-03-1997
		US 6001834 A	14-12-1999
		US 5559117 A	24-09-1996
		US 5574032 A	12-11-1996
		US 5648363 A	15-07-1997
		US 5624927 A	29-04-1997
		US 5607945 A	04-03-1997
		US 5583145 A	10-12-1996